REMARKS

Applicants wish to thank the Examiner for his consideration of the prior response and arguments and removal of the indefiniteness rejection of point 14 of the previous Office Action.

Claims 1-18, 20-46, 48-57, 150-153, 155-157, 165-166, and 171-173 are pending.

The Applicants have added new claim 174. Support for new claim 174 can be found throughout the specification, in particular at p. 41, lines 7-12 and p. 64, line 4 – p. 65, line 22. Additionally, the Applicants have amended claims 4-6 to depend from new claim 174.

All pending claims stand rejected.

I. INTRODUCTION

The breakthrough of this current invention relates to the ability to take compounds that are not orally bioavailable or liver specific and transform them into compounds that have good oral bioavailability and high liver specificity. This invention relates to novel prodrugs, *i.e.*, substituted cyclic 1,3 propanyl ester technology that can be applied to compounds of the form $MP(O)(NHR^6)O^-$, MPO_3^{2-}, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$ that are biologically active agents but are not FBPase inhibitors. The focus of the invention is not on M, as the invention is broadly applicable to a variety of Ms. The Applicants are not claiming compounds of the form $MP(O)(NHR^6)O^-$, MPO_3^{2-}, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$. This invention is technology to be used with known compounds of the form $MP(O)(NHR^6)O^-$, MPO_3^{2-}, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$ that are biologically active agents but are not FBPase inhibitors and also such discovered in future.

II. EXAMINER'S GENERAL COMMENTS REGARDING THE CHABALA DECLARATION (POINTS 3-8)

During the Interview on September 10, 2003, Applicants discussed that the term "prodrug" is well-understood and enabled such that many issued patents use this "prodrug" language in the claims. Examiner Shah indicated that this language does meet the requirements for definiteness, written description, and enablement. In view of this, the Applicants do not understand why the Examiner continues to reject the claims based on the use of the term "prodrug."

To summarize the rejections, we note that the Examiner begins the Office Action with some general comments regarding Dr. Chabala's declaration. The Examiner states that the declaration is

insufficient to overcome the indefiniteness rejections of claims 1-3, 7, 9, 11-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173 in Points 5-8 of the previous office action because:

> The only evidence supplied is the occurrence of the term "biologically active agent" in other US Patents. Firstly, Rule 132 declarations are a mechanism to introduce evidence and must set forth facts, not merely conclusions, *In re Pike* 84 USPQ 235. Allegations are not probative, *In re Brandstadter* 179 USPQ 286, *In re Knowlton* 183 USPQ 33. Secondly, the indefiniteness remains despite what was allowed in another case. The U.S. Court of Customs and Patent Appeals wrote *In re Giolito* 188 USPQ 645: "We reject appellants' argument that the instant claims are allowable because similar claims have been allowed in a patent. It is immaterial whether similar claims have been used by others." (citations omitted)(Office Action pp. 2-3)

The Examiner says the declaration is insufficient to overcome the indefiniteness rejections of claims 1-3, 7, 9,11-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173 in Points 9-11 of the previous office action because:

> Undue experimentation is not a test for indefiniteness and in any case no weight is given to an opinion affidavit on the issue of ultimate legal conclusion...While testing for FBPase activity may or may not be routine, defining something by what is not, does not address that vast array of molecules that are neither biologically active nor FBPase inhibitors. This definition does not distinguish the array of molecules that are biologically active but not FBPase inhibitors. This also avoids the essential point of the rejection that the structures of these functionally defined compounds are simply unknown. (Office Action pp. 3-4)

The Examiner says the declaration is insufficient to overcome the enablement rejections of claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165-166, and 171-173 in Point 12 of the previous office action because:

> Dr. Chabala points to parts of the specification teaching how to make the compounds, which are within the scope of enablement material. Enablement is a legal issue and no weight is afforded his opinion that the remaining scope of compounds are enabled. (citations omitted)(Office Action p. 4)

The Examiner says the declaration is insufficient to overcome the lack of written description rejections of claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165-166, and 171-173 in Point 13 of the previous office action because:

> Written description is a legal issue and no weight is afforded to his opinion that the claims are fully described.(citations omitted)(Office Action p. 4)

The Examiner says the declaration is insufficient to overcome the enablement rejections of claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165-166, and 171-173 in Points 14-15 of the previous office action because:

> Dr. Chabala points to page 103 of the specification, which teaches synthesis of a number of compounds of formula I. There is no new evidence presented. However, that passage in question is silent as to the essential question of whether such compounds are, in fact, prodrugs or of making any prodrug of a molecule of formula (I). The passage provides no experimental method of determining if they are prodrugs. The scope of possible prodrugs is large and the declaration must present a showing which is commensurate in scope to the claimed subject matter. (citation omitted)(Office Action p. 5)

The Examiner says the declaration is insufficient to overcome the indefiniteness, lack of written description, and enablement rejections of claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165-166, and 171-173 in Points 15-16 of the previous office action because:

> Again there is no evidence presented, only the assertion that search for prodrugs is routine in pharmaceutical companies. Rule 132 declarations are a mechanism to introduce evidence and must set forth facts, not merely conclusions, *In re Pike* 84 USPQ 235. Mere allegations are not probative, *In re Brandstadter* 179 USPQ 286, *In re Knowlton* 183 USPQ 33. (Office Action pp. 5-6)

The Applicants wish to address the a Examiner's comments. Firstly, the Examiner says that he will not give any weight to an affidavit addressing the ultimate legal conclusion. Although indefiniteness is a question of law *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1377, 55 USPQ2d 1279 (Fed. Cir. 2000)("as with claim construction, a determination under either portion of section 112, paragraph 2, is a question of law that we review de novo."), written description is a question of fact. *Union Oil of California v. Atlantic Richfield Co.*, 208 F.3d 989, 996, 54 USPQ2d 1227 (Fed. Cir. 2000)(stating that the primary consideration is factual). Therefore an opinion on the written description issue does not go to a legal conclusion.

The Applicants point to the use of the term "biologically active" in other patents in order to show that the term is widely used and understood by persons of ordinary skill in the art.

The Examiner appears to presume that the claims are indefinite unless the Applicant can identify every compound that falls within the scope of the claims. That argument is legally flawed. One skilled in the art must be able to determine whether a given compound falls within the scope of the claims. There is no requirement that anyone determine and give structures for all the compounds that fall within the scope of the claims in order for the claims to be definite.

III. REJECTIONS BASED ON THE TERM "PRODRUG"

A. Claims 1-18, 20-46, 48-57, 150-153, 155-157, 165, and 171-173 are rejected as indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention (Point 12)

This rejection is respectfully traversed.

The Examiner finds the term "prodrug" to be indefinite. The Examiner states:

> The issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of formula I, but upon metabolism in the body are converted to active compounds falling with the structural scope of formula I. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug." (Office Action p. 14)

During the Interview on September 10, 2003, Applicants discussed that the term is well-understood and enabled such that many issued patents use this "prodrug" language in the claims. Examiner Shah indicated that this language does meet the requirements for definiteness, written description, and enablement.

In view of this, the Applicants do not understand why the Examiner continues to reject the claims based on the use of the term "prodrug." The Applicants again wish to again note that there is nothing inherently wrong with the use of functional language. MPEP § 2173.05(g). In fact the use of functional language has explicitly been approved by the Court of Appeals. When discussing functional language in *Swinehart*, the Court said:

> In our view, there is nothing intrinsically wrong with the use of such a technique in drafting patent claims. Indeed, we have even recognized in the past the practical *necessity* for the use of functional language. *In re Swinehart and Sfiligoj*, 169 U.S.P.Q. 226, 228 (C.C.P.A. 1971).

Furthermore, MPEP § 2173.01 states:

> Applicants may use functional language, alternative expressions, negative limitations, or any style of expression or format of claims which makes clear the boundaries of the subject matter for which the protection is sought. As noted in *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971), a claim may not be rejected solely because of the type of language used to define the subject matter for which patent protection is sought.

For example, *In re Barr*, the U.S. Court of Customs and Patent Appeals approved the use of functional language in defining the term "incapable of forming a dye with said oxidized developing agent." *See In re Barr*, 170 U.S.P.Q. 330, 337 (C.C.P.A. 1971). The Court went on to say that:

> In summary, we hold that an applicant may invoke the third paragraph of section 112 to justify the specification of one or more elements of a claimed compound in "functional" terms, and that those "functional" terms may be "negative." The real issue in any such case is not whether the recital is "functional" or "negative," but whether the recital sets definite boundaries on the patent protection sought - that is, whether those skilled in the relevant art can determine what the claim does or does not read on. Judged by this standard, we think it clear that the controverted language complies with the second paragraph of section 112. *Id.*

Furthermore, a "limited use of terms of effect or result, which accurately define the essential qualities of a product to one skilled in the art, may in some instances be permissible and even desirable." *In re Fuetterer*, 138 USPQ 217, 222 (C.C.P.A. 1963)(quoting *General Electric Co. v. Wabash Appliance Corp.*, 37 USPQ 466, 469 (U.S. 1938)).

The present situation is similar to the *In re Fuetterer* case. In that case, the examiner and the Board rejected certain composition claims as indefinite, ambiguous, unduly broad, and functional, in part because the term "inorganic salts" was defined in a functional way. *Id.* at 218-219. The examiner stated that:

> "Inorganic salt" reads on literally thousands of materials, many of which would *not be operative* for applicant's purpose. For example, some salts *could* readily react with other ingredients in the composition while other salts *could* be corrosive or destructive of the rubber. This recitation is functional since it merely describes how the salt functions as the surface of the tire wears away. *Id.* at 220.

First, the Court found that use of functional language was proper. *Id.* at 222. Then the Court went on to say that the claims were not unduly broad. *Id.* at 223. The Court stated:

> in the words of the *second* paragraph of section 112, "applicant regards as his invention" the combination with his other tread ingredients of *any* inorganic salt *capable* of "maintaining the carbohydrate, the protein, or mixture thereof, in colloidal suspension* * *." It is exactly this combination which appellant has particularly pointed out and *distinctly claimed* in compliance with the *second* paragraph of section 112...Appellant's invention is the *combination* claimed and not the discovery that certain inorganic salts have colloidal suspending properties. We see nothing in the patent law which requires appellant to discover which of all those salts have such properties and which will function in combination. *Id.*

The Court went on to point out that there was no "undue burden" caused by the functional language of the claims:

> The Patent Office would require him to do research on the "literally thousands" of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented and is not claiming colloidal suspending agents but tire stock composed of a combination of rubber and other ingredients. *Id.*

Although not directly on point, since the claim in *Fuetterer* was a combination claim, the C.C.P.A. held that the same reasoning applies to elements in claims for compounds. *See In re Barr*, 170 U.S.P.Q. at 336 (stating that although *Fuetterer* was not directly on point "we feel that its rationale, if not its holding, is controlling here.").

As in Fuetterer, it would be an undue burden on the Applicant to list each and every suitable prodrug. The desirability of functional language in these claims is clear.

As stated in *Barr*, the real issue is whether the Applicants have set definite boundaries on the patent protection sought. A person of ordinary skill in the art knows what a prodrug is. A person of ordinary skill in the art would also understand what the boundaries of the invention are, particularly when the claims are viewed in light of the specification. According to MPEP § 2173.02, when "reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claims as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph." Accordingly, there is nothing wrong with defining the term "prodrug" in a functional manner. Nothing requires that the Applicants list each and every suitable prodrug. All that is required is that one of ordinary skill in the art can determine the scope of the claims.

As explained by organic and medicinal chemist Dr. John C. Chabala:

> Contrary to the Examiner's position, a person of ordinary skill in the art can readily determine what is or what is not a prodrug of the current invention. The tests for whether a compound is or is not a prodrug are routine, do not require undue experimentation, and were well-known in the art as of March 1999. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation. [Chabala Decl. ¶ 17]

Therefore, the Applicants respectfully submit that claims 1-18, 20-46, 48-57, 150-153, 155-157, 165-166 and 171-173 are definite and request withdrawal of the rejection.

B. Claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173 are rejected for failing to meet the written description requirement (Point 13)

This rejection is respectfully traversed.

The Examiner argues that "Applicants' claims are drawn to any derivative of the compounds of formula I with a specific biological property. What are the structures of these prodrugs?" (Office Action p. 15)

During the Interview on September 10, 2003, Applicants discussed that the term is well-understood and enabled such that many issued patents use this "prodrug" language in the claims. Examiner Shah indicated that this language does meet the requirements for definiteness, written description, and enablement. In view of this, the Applicants do not understand why the Examiner continues to reject the claims based on the use of the term "prodrug."

Examiner McKenzie has indicated in a previous interview (November 20, 2002) that if the indefiniteness rejection is removed, the written description rejection would also be removed as to these claims. In light of the argument above, the Applicants believe that these claims are definite and also satisfy the written description requirement.

Additionally, organic and medicinal chemist Dr. John C. Chabala has stated that:

> Contrary to the Examiner's position, a person of ordinary skill in the art can readily determine what is or what is not a prodrug of the current invention. The tests for whether a compound is or is not a prodrug are

> routine, do not require undue experimentation, and were well-known in the art as of March 1999. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation. [Chabala Decl. ¶ 17]

Therefore, the Applicants respectfully submit that claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173 are definite and request withdrawal of the rejection.

C. Claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173 are rejected as lacking enablement (Point 14)

This rejection is respectfully traversed.

The Examiner states:

> Directions to a team of pharmacologist, medicinal chemists, and pharmacokinetic experts of how to search for Applicants prodrugs hardly constitute direction to the process chemist of how to make these claimed compounds. (Office Action p. 15)

The Examiner goes on to discuss the factors to be considered:

> a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental uncertainty. For a compound to be a prodrug, it must meet three tests. It must be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical setting requires a large degree of experimentation.
>
> b) There is extensive discussion of the concept of prodrug and how to search for and prepare compounds of formula I that are themselves prodrugs. The direction concerning making the prodrugs, which liberate the compounds of formula, I is found in lines 13-16, page 30. This passage just states Applicants intent to do so.
>
> c) There is no working example of a prodrug which produces a compound of formula I. The biological data in the passage spanning line 10, page 115 to line 26, page 126, do not demonstrate that even any of the compounds of formula I are themselves prodrugs. The only *in vivo*

experiments, Examples O-S appear to be prophetic and not working examples.

d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body.

e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the lefts side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of pharmaceutical chemists and metabolism experts.

g) The lack of predictability in finding prodrugs was discussed above.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 136 as well as the presently unknown list of potential prodrug derivatives embraced by claim 136.

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug. (Office Action pp. 16-18)

During the Interview on September 10, 2003, Applicants discussed that the term is well-understood and enabled such that many issued patents use this "prodrug" language in the claims. Examiner Shah indicated that this language does meet the requirements for definiteness, written description, and enablement. In view of this, the Applicants do not understand why the Examiner continues to reject the claims based on the use of the term "prodrug."

The Applicants are not exactly clear on which undue experimentation factors the Examiner is attempting to address in all of the above points. According to MPEP § 2164.01(a), the factors to be considered include a) the breadth of the claims; b) the nature of the invention; c) the state of the prior art; d) the level of one of ordinary skill in the art; e) the level of predictability in the art; f) the amount of direction provided by the inventor; g) the existence of working examples; and h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

As explained by Dr. Erion in his Declaration submitted with the Response mailed April 10, 2003, finding a prodrug is not an empirical exercise, in fact "a person of ordinary skill in the art can readily determine what is or what is not a prodrug of the current invention. The tests for making such determinations are routine and well-known in the art." (Erion Decl. ¶ 4). Furthermore, prodrug technology is well understood in the art.

In fact, the Applicants have provided structural guidance as to what is meant by the term "prodrug." As explained by Dr. Erion

> As defined at p. 15 of the specification a prodrug is a compound that undergoes a chemical modification to form a biologically active molecule or a precursor to the biologically active drug. There are many commonly known prodrugs. For example, a compound may have a free hydroxyl group on it. A common prodrug of a hydroxyl is an ester. Esters are often quickly broken down within the body to produce the compound with the free hydroxyl. In this example, the ester is the prodrug. In general, each functional group, *e.g.* hydroxyl, thiol, amine, carboxylic acid, has a set of well described prodrugs that have proven useful for masking the functional group in a manner that enables improved oral bioavailability, improved pharmacokinetics, improved distribution, or other properties readily observable during testing in animals and man. (Erion Decl. ¶ 4).

In addition, the specification gives examples for the preparation of prodrugs of this invention. (*See* pp. 89-95 and Examples 12 and 13, pp. 113-114). According to MPEP § 2164.01(b), "As long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." Dr. Erion explains that "a person of ordinary skill in the art could routinely prepare prodrugs of the invention particularly in view of the general procedures for prodrug preparation given at pp. 89-95 of the specification and by the definition of the term "prodrug" at p. 15 of the specification." (Erion Decl. ¶ 8).

The Examiner's complaint there are no "working" examples of prodrugs is not a recognized ground in either the MPEP or caselaw for patentability of claims. The Examiner admitted that the specification contains paper examples for prodrug activity. The MPEP and caselaw recognize the adequacy of paper examples to support claims. MPEP § 2164.02 ("Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether a working example is disclosed."); *Gould v. Quigg*, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)("The mere fact that something

has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." citation omitted).

The Examiner also points to the research program outlined in *Wolff* and to the phrase "extensive development must be undertaken to find the correct chemical modification" in *Banker* as "an invitation to open-ended and potentially inconclusive research." (Office Action p. 31). The Applicants respectfully disagree with the Examiner's interpretation of these textbook sections. The Examiner appears to take these quotations out of context. For instance, the standard for getting a drug approved for use in humans by the FDA is a completely different standard from that required for patentability.

In any event, the Applicants are not clear as to why the Examiner finds these textbooks persuasive. The enablement requirement does not require that there be no experimentation. As stated in M.P.E.P. § 2164.01:

> The fact that some experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation...The test of enablement is not whether any experimentation is necessary, but whether if experimentation is necessary, it is undue. M.P.E.P. § 2164.01 (internal citations omitted)

In fact, Dr. John C. Chabala has stated that:

> Contrary to the Examiner's position, a person of ordinary skill in the art can readily determine what is or what is not a prodrug of the current invention. The tests for whether a compound is or is not a prodrug are routine, do not require undue experimentation, and were well-known in the art as of March 1999. Typically prodrugs are evaluated by first establishing assays that monitor production of the biologically active drug. This is typically accomplished using HPLC or HPLC coupled with mass spectroscopy. All techniques are routine for pharmaceutical companies and do not comprise undue experimentation. [Chabala Decl. ¶ 17]

Therefore, the Applicants respectfully request withdrawal of the rejection that claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173 are not enabled.

D. General Comments by the Examiner (Point 14)

The Examiner says that he will discuss the three rejections based on "prodrug" together. He then goes on to discuss what he considers to be the Applicants six arguments regarding the rejections. The Examiner says:

> Firstly, while functional language can be used, prodrug lacks the critical attribute of possessing a clear, and well-understood connection between structure and function. That nexus must be present before a functional term can be used. Secondly, while the skilled chemist known[sic] what a prodrug is suppose to do, he most certainly does not know the structure of the derivate that conveys this property to any particular drug. He does not know what it "is", but rather what it does.
>
> Thirdly, concerning arguments about similar claims in issued US Patents, this is not persuasive. (citations omitted)
>
> Fourthly, the declaration was discussed above. Fifthly, all Wands eight factors were considered in reaching the conclusion of undo[sic] experimentation. (citations omitted)
>
> Sixthly, concerning the alleged routine nature of prodrug synthesis and characterization, the references cited by the Examiner state the opposite. There is no magic derivative that converts a drug into a prodrug. Only after the extensive experimentation can any derivative drug be shown to be a prodrug. (Office Action pp. 18-20)

The Applicants traversed the rejections separately above, but now address these comments together below.

During the Interview on September 10, 2003, Applicants discussed that the term is well-understood and enabled such that many issued patents use this "prodrug" language in the claims. Examiner Shah indicated that this language does meet the requirements for definiteness, written description, and enablement. In view of this, the Applicants do not understand why the Examiner continues to reject the claims based on the use of the term "prodrug."

The Applicants did not say that there were no standard procedures for making prodrugs. They said that there is no requirement that any textbook contain a recipe for making "prodrugs" of the Applicants' invention. The specification describes the preparation of prodrugs of this invention. (*See* pp. 89-95 and Examples 12 and 13, pp. 113-114). As Dr. Erion has explained "a person of ordinary skill in the art could routinely prepare prodrugs of the invention particularly in view of the general procedures for prodrug preparation given at pp. 89-95 of the specification and by the definition of the term "prodrug" at p. 15 of the specification." (Erion Decl. ¶ 8).

The Applicants explained at the Interview and now respectfully reiterate that the use of term "prodrug" in the claims of over 300 patents is material, because it shows that the term is commonly used and well-understood by persons of ordinary skill in the art.

The Applicants respectfully request withdrawal of all rejections based on the term "prodrug."

IV. REJECTIONS BASED ON "M IS SELECTED FROM THE GROUP THAT ATTACHED TO PO_3^{2-}, $P_2O_6^{3-}$, $P_3O_9^{4-}$ OR $P(O)(NHR^6)O^-$ IS A BIOLOGICALLY ACTIVE AGENT BUT IS NOT AN FBPase INHIBITOR, AND IS ATTACHED TO THE PHOSPHORUS IN FORMULA I VIA A CARBON, OXYGEN, SULFUR OR NITROGEN ATOM"

A. Claims 1-3, 7, 9, 11-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166 and 171-173 are rejected as indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention (Point 9)

This rejection is respectfully traversed.

The Examiner states:

> The phrase in lines 20-21, page 2, claim 1, "M is selected from...is biologically active but is not an FBPase inhibitor" is indefinite. What is the structure of the radical M? What do the Applicants intend by "biologically active agent? How active and active as what?
>
> The Examiner suggest using chemical formulas to define the structure of the claimed "M" radical. (Office Action p. 6)

The specification at pp. 21-22 defines "biologically active drug or agent" as:

> The term "biologically active drug or agent" refers to the chemical entity that produces the biological effect. In this invention, biologically active agents refers to $M\text{-}PO_3^{2-}$, $M\text{-}P(O\text{-})NHR^{6-}$, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$ where M can be the same M as in the parent drug or a metabolite. pp. 21-22

According to MPEP § 2173.02, the definiteness of claim language must not be analyzed in a vacuum, but in light of:

> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The Applicants believe that a person of ordinary skill in the art would understand the meaning of the term "biologically active agent" especially when it is read in light of the specification.

As Dr. Chabala explains in his Declaration:

> As a medicinal chemist, I understand the term "biologically active agent." In addition, I believe a person of ordinary skill in the art would be guided by the specification, which defines the term "biologically active agent" at pp. 21-22. The practicing medicinal chemist recognizes that the effect can be exerted on any component or sets of components of a living organism either within the complete organism or as separated components, such as its constitutive molecules, organelles, cells, tissues, organs, up to and including the complete organism. [Chabala Decl. ¶ 7]

Dr. Chabala goes on to explain:

> I am aware that there are at least 300 patents issued from 1976 to the present that use the term "biologically active agent" in the claims. In general, the term "biologically active agent" is not defined in the specification in these patents. (see e.g., U.S. Patent Nos. 6,602,975; 6,264,990; 5,980,551; 5,855,608; 5,783,211; 5,462,990; 5,028,424; 4,976,968; 4,704,942; and 3,975,350). I believe that this supports my conclusion that the term "biologically active agent" is well understood by a person of ordinary skill in the art. [Chabala Decl. ¶ 8]

A person of ordinary skill in the art understands the scope of the claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165-166, and 171-173. Dr. Chabala states:

> Contrary to the Examiner's position, a person of ordinary skill in the art would have understood what was claimed as of March 5, 1999. As a medicinal chemist reading claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173, I clearly understand how to determine which compounds would be included and excluded by the claims. I believe that persons of ordinary skill in the art would also know how to determine whether a compound is within or outside the scope of the claims. The tests for whether a compound is or is not a biologically active agent that is not an FBPase inhibitor of this invention, do not require undue experimentation, and were well-known in the art as of March 5, 1999. [Chabala Decl. ¶ 6]

Therefore, the Applicants respectfully submit that claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165-166, and 171-173 are definite and request removal of the rejection.

B. Claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165-166, and 171-173 are rejected for failing to meet the written description requirement (Point 10)

This rejection is respectfully traversed.

The Examiner states:

> The issue concerning the meaning of the phrase, "M is selected from...is a biologically active agent but is not an FBPase inhibitor" is discussed above. Claims 1-3, 7, 9-18, 20-46, 48-53, 150-153, 155-157, 165, 166, and 171-173 do not contain a complete generic formula. (Office Action p. 7)

After citing the MPEP, the Examiner goes on to say:

> Applicants have made no assertion that there is any correlation between the biological function of radical "M" and its structure.
>
> As discussed above the phrase ""M is selected from...is a biologically active agents but is not an FBPase inhibitor" is not art recognized in synthetic organic chemistry. (Office Action p. 8)

After citing the MPEP again, the Examiner says:

> Thus, the chemist of ordinary skill in the art, who would make Applicants' compounds, would not know what "M is selected from...is a biologically active agents but is not an FBPase inhibitor". That chemist would not have understood the inventor to be in possession of the claimed compounds at the time of filing.
>
> This case was filed before Applicants had a clear idea of the structures of their desired compounds, how to make their compounds, and use of the compositions made from them. The specification provides broad areas of future research and speculation, inviting undue experimentation in learning how to use Applicants' invention. Applicants may well now be developing practical applications of their compounds, but the question here is what application they possessed at the time of filing. Anything is possible but as the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences wrote in *Bindra v. Kelly*, 206 USPQ 570 "*Probable* utility does not establish practical utility. Practical utility can, in our view, be established only by actual testing therefore, or by establishing such facts as would be convincing that such utility could be "foretold with certainty." *Blicke v. Treves*, supra, 112 USPQ at 475."
>
> Applicants are reminded of what the U.S. Court of Appeals Federal Circuit wrote in University of California v. Eli Lilly and Co. 43 USPQ2d 1398, "In claims involving chemical materials, generic formulae usually

> indicated with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. (citation omitted) "It is only a definition of a useful result rather than a definition of what achieves that result." "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention." (citation omitted)(Office Action pp. 9-10)

The Applicants note that M is not an essential feature in the way the Examiner appears to mean. The breakthrough of this current invention relates to novel prodrugs, *i.e.*, substituted cyclic 1,3 propanyl ester technology that can be applied to compounds of the form $MP(O)(NHR^6)O^-$, MPO_3^{2-}, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$ that are biologically active agents but are not FBPase inhibitors. The Applicants are not claiming compounds of the form $MP(O)(NHR^6)O^-$, MPO_3^{2-}, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$.

The Examiner mistakenly concludes that the Applicants do not understand M because they exclude certain groups by proviso. However, the Applicants must understand M if they can exclude certain groups. In fact, the M groups were excluded here because of certain cytotoxic (anticancer) compounds, such as ifosfamide and cyclophosphamides that are known in the art. (*see e.g.* in Applicants' IDS submitted June 7, 2001, U.S. Patent No. 3,018,302 or EP 0 072 531). The Applicants do not believe that these compounds are included within the scope of the claims, but out of an abundance of caution eliminated such M groups by proviso.

The Examiner also cites the *Lockwood* case to support his contention that M should be identified by structure. (Office Action p. 5). However, *Lockwood* does not say that structures are required in order to satisfy the written description requirement. At issue in the *Lockwood* case was whether a patent (the '335 patent) was entitled to a filing date of an earlier application. *See Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1571 (Fed. Cir. 1997). One of the intervening applications did not describe all of the claimed features. *Id.* at 1572. The Court explained that the problem in Lockwood was that "Lockwood claimed a distinct invention from that disclosed in the specification." *Id.* That is simply not the case here. The specification describes all the limitations of the claims.

The skilled medicinal chemist would understand what is meant by M, because M is defined in a functional manner and the skilled medicinal chemist can therefore determine what is included within and without the scope of the claims. Dr. Chabala explains that a person of ordinary skill in the art can determine what compounds fall within or without the scope of the claims without undue experimentation:

> By March, 1999, it was a matter of routine testing to determine whether or not a given compound is a biologically active agent that is not an FBPase inhibitor. The specification at p.21 indicates that an FBPase inhibitor is a compound that inhibits the human enzyme fructose-1,6-bisphosphatase with an IC50 of at least 100 μM and lower glucose in a normal 18-hour fasted rat following a 100 mg/kg dose i.v. Simple spectrophotometric assays can be used to determine enzymatic activity. Such assays were well-known in March 1999. [Chabala Decl. ¶ 9]
>
> High Throughput Screening enables rapid evaluation of large numbers of compounds (1000s per day). As of March, 1999, such screens were widely employed. For instance, a spectrophotometric enzymatic assay would have been and is easily employed in high throughput screening. [Chabala Decl. ¶ 10]
>
> Given the guidance in the specification and the routine nature of the testing involved, one can easily determine what compounds fall within the scope of the claims with routine experimentation. Once a compound has been identified as a compound of the invention, as of March, 1999, a person of ordinary skill in the art could determine its purity and confirm its structure by routine liquid chromatography coupled directly to mass spectrometry as was and is commonly done. [Chabala Decl. ¶ 11]

During the Interview on September 10, 2003, the Examiner expressed his concerns regarding PTO policy in light of the *University of Rochester* Cox 2 inhibitor district court decision. At that time, the Applicants distinguished that case and emphasized the amount of data taught in the current application. The Applicants take this opportunity to reiterate and elaborate on their position.

The Examiner's reliance on the *University of Rochester* case is misplaced. In the *University of Rochester* case, the patent claimed "a method for selectively inhibiting PGHS-2 activity in a human host in which 'the activity of PGHS-1 is not inhibited.'" *University of Rochester v. G.D. Searle & Co., Inc.*, 249 F. Supp. 2d 216, 219 (W.D.N.Y. 2003). The Defendants claimed that the patent did not meet the written description and enablement requirements. *Id.* at 220. In particular, the Defendants said that "while the patent calls for use of a "compound" that selectively inhibits PGHS-2 activity, the patent

specification does not identify any such compound." *Id.*(emphasis added). The Court believed that the issue in this case was "whether a written description of a claimed method of treatment is adequate where a compound that is necessary to practice that method is described only in terms of its function, and where the only means provided for finding such a compound is essentially a trial and error process." *Id.* at 221. The Court found that there was no "suggestion that the inventors had identified so much as one compound that would be suitable for use in practicing the claimed invention." *Id.* at 225(emphasis added). "At best, it simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work." *Id.* at 224.

The Court said:

> I do not hold that it is a *sine qua non* that the patent set forth the exact chemical structure of the compounds in question. It is only necessary that the patent set forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed. *Id.* at 227 (emphasis added)

The Court recognized that the inventors had realized that finding a compound that would specifically target the activity of PGHS-2 would be beneficial. However, the Court believed that the inventors did not "succeed in taking the last, critical step of actually isolating such a compound, or at least of developing the process through which one skilled in the art would be directly led to such a compound." *Id.* at 228.

The Court said "The patent describes how to test compounds to determine whether they work, but it does not set forth any procedure that will necessarily lead to discovery of such a compound, nor does it even identify any particular class of compounds that contains at least one suitable member." *Id.* at 228.

The Court felt that the inventors "had neither possession nor knowledge of" a compound that selectively inhibited PGHS-2 activity. *Id.* at 229.

> Even if the inventors were reasonably certain that the necessary compound existed and could eventually be found, there is no showing in the patent that they knew that to be a fact. In short, without possession or at least knowledge, of such a compound, or of a method certain to yield such a compound, the inventors could not have possessed the claimed invention, *i.e.*, a method of treatment using the compound. *Id.* at 229

The Court also found that the patent did not comply with the enablement requirement. *Id.* at 232. The Court acknowledged that the patent described "how to conduct assays 'for the screening of drug actions on both' PGHS-1 and PGHS-2." and "what to do with 'any of the identified compounds' once

they *have* been identified as selective PGHS-2 inhibitors." *Id.* at 232. The Court believed that the patent did not "provide the necessary link between those two steps; actually finding a compound that works. It provides precious little guidance in the way of selecting a particular compound, or even of narrowing the range of candidates in order to find a suitable compound without the need for undue experimentation." *Id.* at 233.

In the end the Court summarized: "In short, although the '850 patent describes an assay for determining whether a given compound possesses certain desired characteristics, and identifies some broad categories of compounds that *might* work, these descriptions, without more precise guidelines, amount to little more than 'a starting point, a direction for further research.'" *Id.* at 235.

The Federal Circuit confirmed the lower Court's granting of summary judgment of failure to comply with the written description requirement. *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 917 (Fed. Cir. 2004). The Federal Circuit emphasized that "it is undisputed that the '850 patent does not disclose any compounds that can be used in its claimed methods...No compounds that will perform the claimed method are disclosed, nor has any evidence been shown that such a compound was known." *Id.* at 927 (emphasis added). The Court then went on to say: "As pointed out by the district court, however, the '850 patent does not disclose just "*which* 'peptides, polynucleotides, and small organic molecules' have the desired characteristic of selectively inhibiting PGHS-2."...Without such disclosure, the claimed methods cannot be said to have been described." *Id.*

Unlike the *University of Rochester* case, the Applicants here have provided data in the application. Indeed, the Applicants have identified compounds of the invention. For instance, the dependent claims clearly identify specific groups MH. In claim 8, MH is "is selected from the group consisting of ACV, GCV, 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine, and (R)-9-(3,4-dihydroxybutyl)guanine."

Additionally, the Applicants have provided biological data for compounds of the present invention. In Example F (pp. 118-19), the Applicants demonstrate that compound 1.3 is activated by recombinant CYP3A4. In Example G (pp. 119-120), the Applicants demonstrate the activation of compounds 3.1 and 3.2 in isolated rat hepatocytes. In Example I (pp. 120-121), the Applicants demonstrate the inhibition of glucose production by compound 1.3. In Example J, the Applicants demonstrate the activation of compounds 1.7 and 2.1 in induced rat hepatocytes. In addition, the Applicants have provided instructions for preparing compounds of formula 1 at pp. 89-98.

Applicants maintain that the functional language in the current application is much more analogous to the *In re Fuetterer* case. In that case, the examiner and the Board rejected certain composition claims as indefinite, ambiguous, unduly broad, and functional, in part because the term "inorganic salts" was defined in a functional way. *In re Fuetterer*, 138 USPQ 217, 218-219. The examiner stated that:

> "Inorganic salt" reads on literally thousands of materials, many of which would *not be operative* for applicant's purpose. For example, some salts *could* readily react with other ingredients in the composition while other salts *could* be corrosive or destructive of the rubber. This recitation is functional since it merely describes how the salt functions as the surface of the tire wears away. *Id.* at 220.

First, the Court found that use of functional language was proper. *Id.* at 222. Then the Court went on to say that the claims were not unduly broad. *Id.* at 223. The Court stated:

> in the words of the *second* paragraph of section 112, "applicant regards as his invention" the combination with his other tread ingredients of *any* inorganic salt *capable* of "maintaining the carbohydrate, the protein, or mixture thereof, in colloidal suspension* * *." It is exactly this combination which appellant has particularly pointed out and *distinctly claimed* in compliance with the *second* paragraph of section 112...Appellant's invention is the *combination* claimed and not the discovery that certain inorganic salts have colloidal suspending properties. We see nothing in the patent law which requires appellant to discover which of all those salts have such properties and which will function in combination. *Id.*

The Court went on to point out that there was no "undue burden" caused by the functional language of the claims:

> The Patent Office would require him to do research on the "literally thousands" of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented and is not claiming colloidal suspending agents but tire stock composed of a combination of rubber and other ingredients. *Id.*

Although not directly on point, since the claim in *Fuetterer* was a combination claim, the C.C.P.A. held that the same reasoning applies to elements in claims for compounds. *See In re Barr*, 170 U.S.P.Q. 330, 336 (C.C.P.A. 1971) (stating that although *Fuetterer* was not directly on point "we feel that its rationale, if not its holding, is controlling here.").

As in *Fuetterer*, it would be an undue burden on the Applicant to list each and every suitable compound. The desirability of functional language in these claims is clear.

In re Barr, the U.S. Court of Customs and Patent Appeals approved the use of functional language in defining the term "incapable of forming a dye with said oxidized developing agent." *In re Barr*, 170 U.S.P.Q. at 337. The Court went on to say that:

> In summary, we hold that an applicant may invoke the third paragraph of section 112 to justify the specification of one or more elements of a claimed compound in "functional" terms, and that those "functional" terms may be "negative." The real issue in any such case is not whether the recital is "functional" or "negative," but whether the recital sets definite boundaries on the patent protection sought - that is, whether those skilled in the relevant art can determine what the claim does or does not read on. Judged by this standard, we think it clear that the controverted language complies with the second paragraph of section 112. *Id.*

Thus, the real issue in definiteness under section 112 is to provide notice to the art so that they can determine if the compound they have is within or outside the scope of the claims. *See e.g., Morton Int'l, Inc. v. Cardinal Chem. Co.* 5 F.3d 1464, 1470 (Fed.Cir. 1993). A person of ordinary skill in the art would also understand what the boundaries of the invention are, particularly when the claims are viewed in light of the specification.

In addition, numerous other cases have found that the use of functional language is acceptable. *See e.g. In re Herschler*, 200 U.S.P.Q. 711, 717 (C.C.P.A. 1979)(disagreeing with the solicitor who said that a single example of a steroid in the specification could not describe the class of steroids claimed in a functional manner); *In re Edwards*, 196 U.S.P.Q. 465, 467 (C.C.P.A. 1978)(stating that the application is "not intrinsically defective merely because appellants chose to describe their claimed compound by the process of making it); *In re Mattison*, 184 U.S.P.Q. 484, 486 (C.C.P.A. 1975)(saying "General guidelines are disclosed for a proper choice of the substituent Ep together with a representative number of examples."); *Ex parte Schundehutte*, 184 U.S.P.Q. 697 (Bd. Pat. App. & Int. 1974).

In particular, examples of the claimed compounds are often found to be sufficient to guide a person of ordinary skill in the art when it comes to functional claims. For instance, in the *Ex parte Schundehutte* case, the Examiner rejected a claim which read "A reactive dyestuff of the formula...is the radical of an organic dyestuff in which –N-R'$_1$ is bonded directly to an aromatic nuclear carbon atom of F..." *Ex parte Schundehutte*, 184 U.S.P.Q. at 697. The examiner also found the claim was not enabled and lacked written description, because "examples and other exemplary material in the disclosure is not adequately representative of the area covered by the claims and does not provide 'assurance that all of the compounds falling within the scope of the claims will dye fabrics with asserted properties.'" *Id.* at 698. The Board did not agree that the claims were indefinite saying

> While specific methods of use and/or dyeing properties for each and every species covered by the claims have not been demonstrated as pointed out by the examiner, a disclosure of that extent is not required by statute...In the present case, we believe that those skilled in the art could effectively use the reactive dyestuff compounds of the scope covered by the claims, at least without undue experimentation, from the present written description of the invention in the specification, including the numerous examples therein, and from the art recognized properties of dyestuff compounds and conventional methods of using such compounds which those skilled in the dyestuff art are presumed to know. *Id.*

The Applicants also note that according MPEP § 2163, in order to "satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." In *In re Wetheim*, the Court said "[i]t is not necessary that the application describe the claim limitations exactly, but only so clearly that persons of ordinary skill in the art will recognize from the disclosures that appellants invented processes for including those limitations." *In re Wertheim*, 191 U.S.P.Q. 90, 96 (C.C.P.A. 1976)(internal citations omitted). In *Wertheim*, the disputed term was the limitation "between 35% and 60%." *Id.* at 98. The specification recited a broader range of 25-60%. The Court found that the narrower limitation had adequate written description saying "we are of the opinion that, as a factual matter, persons skilled in the art would consider processes employing a 35-60% solids content range to be part of the appellants' invention." *Id.* The Court went on to say "[i]f lack of literal support alone were enough to support a rejection under § 112, then the statement of *In re Lukach*, that 'the invention claimed does not have to be described in ipsis verbis in order to satisfy the description requirement of § 112,' is empty verbiage." *Id.* (internal citations omitted). Here, as Dr. Chabala has explained a person of ordinary skill in the art would conclude that the inventor had possession of the claimed invention. [Chabala Decl. ¶ 13]

Examiner McKenzie has indicated in a previous interview (November 20, 2002) that if the indefiniteness rejection is removed, the written description rejection would also be removed as to these claims. In light of the argument above, the Applicants believe that these claims are definite and also satisfy the written description requirement.

Therefore, the Applicants respectfully submit that claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166 and 171-173 meet the written description requirement and request withdrawal of the rejection.

C. Claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173 are rejected as lacking enablement (Point 11)

This rejection is respectfully traversed.

The Examiner finds that "the specification while being enabling for making compounds of dependent claims 4-6, 8, 10, 54-55, and 57, does not reasonably provide enablement for making all compounds where M is defined in claim 1." (Office Action pp. 10-11) The Examiner goes on to discuss the factors to be considered:

> a) Preparing any particular compound would first require ascertaining the structure of the M radical, devising a synthesis of the substance, and performing the required synthesis in the laboratory. This is an open-ended and potentially inconclusive degree of experimentation.
>
> b) The direction concerning synthesis is found in the passage spanning line 6, page 89 to line 32, page 98. This passage describes general procedures to be used with M radicals possessing specific functional groups, not every potential M radical.
>
> c) That are twenty-one working examples of synthesis of a compound of formula (I). This is found in the passage spanning line 28, page 103 to line 22, page 107 as well as line 12, page 111 to line 11, page 114.
>
> d) The nature of the invention is chemical synthesis, which involves chemical reactions.
>
> e) The state of the art is instructions to a pharmacologist or physician to search for particular drug hardly constitute directions to the average BS organic chemist of how to make these compounds attached to Applicants cyclic phosphonamide array.
>
> f) The artisan using the Applicants invention to prepare the claimed compounds would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience.
>
> g) Chemical reactions are well-known to unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18.
>
> h) The breadth of all claims included all of the unknown number of compounds of formula I. (Office Action pp. 11-12)

The Applicants believe that a person of ordinary skill in the art would be able to make and use the current invention without undue experimentation.

As stated above in section III.C., the Applicants are not exactly clear on which undue experimentation factors the Examiner is attempting to address in all of the above points. According to MPEP § 2164.01(a), the factors to be considered include a) the breadth of the claims; b) the nature of the invention; c) the state of the prior art; d) the level of one of ordinary skill in the art; e) the level of predictability in the art; f) the amount of direction provided by the inventor; g) the existence of working examples; and h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. However, the Applicants attempt to address each of the Examiner's points below.

a) As the Examiner admits, the specification at pp. 89-98 clearly provides guidance on how to make compounds of the invention. The focus is not on the synthesis of M, but rather on how to make M into a compound of Formula I. As explained, by Dr. Chabala the preparation of compounds of Formula I is routine:

> The specification at pp. 89-98 clearly provides guidance on how to make compounds of the invention. A person of ordinary skill in the art could easily prepare compounds of the invention given the guidance in the specification and by employing other well-known reactions. In general, one is starting with a known MH and allowing it to react to form a phosphoramidate or one is starting with a known MPO_3^{2-} and converting it to a phosphoramidate. Such reactions are routine. [Chabala Decl. ¶ 12]

b) A person of ordinary skill in the art can use routine procedures to prepare compounds not specifically covered by the procedures in the specification. [Chabala Decl. ¶ 12]

c) As stated above, unlike the *University of Rochester* case, the Applicants have provided examples of compounds of this invention.

d) This invention relates to novel prodrugs, *i.e.*, substituted cyclic 1,3 propanyl ester technology that can be applied to compounds of the form $MP(O)(NHR^6)O^-$, MPO_3^{2-}, $MP_2O_6^{3-}$, or $MP_3O_9^{4-}$ that are biologically active agents but are not FBPase inhibitors.

e) and f) The Applicants are not sure why the Examiner is concerned about whether or not the person using the Applicants' invention to prepare the claimed compounds would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. The person preparing the compounds need not be a person of ordinary skill in the art, as this person would be working under the direction of a person of ordinary skill in the art.

g) This is clearly an overstatement as the chemical reactions here are specific and well-known chemical reactions. A statement made by a judge regarding reactions unrelated to the current

application hardly constitutes what a person of ordinary skill in the art would regard as the predictability of the reaction involved in making compounds of the current invention. Dr. Chabala has stated that the reactions are routine and well-understood. [Chabala Decl. ¶ 12]

h) The compounds may not be "known" in the sense of naming each compound of the invention, but a person of ordinary skill in the art can determine through routine experimentation whether or not a compound meets the functional limitation of claim 1. [Chabala Decl. ¶¶ 6 and 9]]

According to MPEP § 2164.01, the test for enablement is whether or not a person of ordinary skill in the art could make and use the invention without undue experimentation. The weighing of all the factors listed by the Examiner does not lead to a conclusion of undue experimentation. Dr. Chabala has clearly stated:

> Contrary to the Examiner's position, a person of ordinary skill in the art would have understood what was claimed as of March 5, 1999. As a medicinal chemist reading claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173, I clearly understand how to determine which compounds would be included and excluded by the claims. I believe that persons of ordinary skill in the art would also know how to determine whether a compound is within or outside the scope of the claims. The tests for whether a compound is or is not a biologically active agent that is not an FBPase inhibitor of this invention, do not require undue experimentation, and were well-known in the art as of March 5, 1999. [Chabala Decl. ¶ 6]

Therefore, the Applicants respectfully submit that claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166 and 171-173 meet the enablement requirement and request withdrawal of the rejection.

D. General Comments by Examiner (Point 11)

The Examiner says that he will discuss the five arguments concerning the three rejections based on M together. He then goes on to say:

> Firstly, there is no confusion about the function of M. What Applicants fail to address is the question of the unknown chemical structure of M. Secondly, Applicants' compounds are to be used for therapy. The phosphorus containing ring of formula I is not the moiety responsible for the pharmacological activity. Applicants admit that the molecule M-H is the active core. It is not logical that M is not essential for the function of the Applicants' compounds since the compounds are to be used for therapy.
>
> Thirdly, Applicants agree that the radical omitted by proviso are not biologically active. While one can only admire Applicants caution

> concerning prior art, why omit something that is not included within the definition of M? Why case the present indefiniteness, if Applicants are so certain they understand the structures of all M-H compounds? Applicants would appear to be agreeing with the Examiner. The fourth point [declaration] was discussed above. As to the fifth point, Applicants simply fail to address the central question, how can a B.S. process chemist make a compound whose structure he does not know. (Office Action pp. 13-14)

The Applicants have traversed each of the rejections separately above and now discuss these five points below.

The point of functional language is that it eliminates the need to put each and every structure that falls within the scope of the claims in the claim. As discussed above and in all the previous responses, there is nothing inherently wrong with the use of functional language.

The Applicants have never said that "M" is not a part of the claimed compounds, only that "M" is not the novel feature of their invention.

The Applicants have **not** admitted that the compounds excluded by proviso are not biologically active. As explained during the interview of November 20, 2002 and in the previous responses, **the excluded compounds are biologically active.**

The Applicants do not understand the Examiner's reference to a BS process chemist. The abilities of the BS process chemist are irrelevant, since the person performing the assays need not be a person of ordinary skill in the art. The person will however be under the guidance of a person of ordinary skill in the art.

V. CLAIMS 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, AND 171-173 ARE REJECTED UNDER 35 USC § 112, SECOND PARAGRAPH, AS BEING INDEFINITE (POINT 16)

The Examiner contends that:

> The phrase in lines 21-22, page 13 "M is not –NH(lower alkyl), -N(lower alkyl)$_2$" is indefinite. M-PO_3^{-2} etc must be biologically active. Are $^{-2}O_3P$-NH(lower alkyl) or $^{-2}O_3P$-N(lower alkyl)$_2$ biologically active? If not, the proviso excluded something that is not present. (Office Action p. 20)

The Examiner then states:

> Applicants state that they excluded the amine radicals out of caution concerning the prior art. While one can only admire Applicants caution concerning the prior art, why omit something that is not included with in the definition of M? Why cause the present indefiniteness, if Applicants are so certain they understand the structures of all M-H compounds? Applicants appear to be agreeing with the Examiner. Removing the proviso can easily solve the issue. (Office Action pp. 20-21)

The Applicants continue to traverse this rejection. As explained during the interview of November 20, 2002 and the last response, **the excluded compounds are biologically active.** Consequently, the proviso does not make the claims indefinite.

Therefore, the Applicants respectfully request withdrawal of the rejection that claims 1-3, 7, 9-18, 20-46, 48-53, 56, 150-153, 155-157, 165-166, and 171-173 are indefinite.

VI. CLAIM 150 IS REJECTED AS INDEFINITE FOR FAILING TO PARTICULARLY POINT OUT AND DISTINCTLY CLAIM THE SUBJECT MATTER WHICH THE APPLICANT REGARDS AS THE INVENTION (POINT 17)

This rejection is respectfully traversed.

The Examiner says:

> Claim 150 provides for transforming "a compound drug having a $-PO_3^{2-}$ ...", but since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. All the word "transforming" does is delineate which molecules are starting materials and which are products. No reactions are named. No conditions essential for any successful chemical reaction are specified. What chemical reactions are being claimed? (Office Action p. 21)

The Applicants again note that this is a process claim that contains the step of transforming a drug having a - PO_3^{2-} or $-P(O)(NHR^6)O^-$ moiety into a compound of formula I.

According to MPEP § 2173.02:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art: and

> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Indeed, it is well established that "claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their 'broadest reasonable interpretation.' " *In re Okuzawa*, 537 F.2d 545, 548, 190 USPQ 464, 466 (C.C.P.A. 1976).

Here, the specification clearly provides guidance to a person of ordinary skill in the art. For example, the specification describes the phosphorylation of an alcohol under Mitsunobu reaction conditions. (p. 94). In the specification starting on p. 103, there are examples of prodrug compounds and general procedures for their preparation. The general procedure for phosphoramidate prodrugs begins with Example 1 and the general procedure for formation of nucleotide prodrugs begins with Example 4 on page 107. A person of skill in the art could use the methods disclosed in the specification to "transform" drugs having - PO_3^{2-} or -$P(O)(NHR^6)O^-$ moieties into compounds of formula I.

In addition, the Applicants need not explain what is known to a person of ordinary skill in the art. According to MPEP § 2173.02, the claim language must be viewed in light of the interpretation that one of ordinary skill in the art would give to it. Since patents are written for persons of skill in the art of a particular field, patents need not contain subject matter that is known to persons of skill in the art. *See S3 Inc. v. nVidia Corp.*, 59 U.S.P.Q. 1745, 1748 (Fed. Cir. 2001). Dr. Chabala explains:

> A person of ordinary skill in the art understands how to transform a drug having a -PO_3^{2-} or -$P(O)(NHR^6)O^-$ moiety into a compound of formula I by using straightforward and well-known reactions. The specification clearly provides guidance (starting at p. 103) on how to prepare prodrug compounds of this invention. The general procedure for phosphoramidate prodrugs begins with Example 1 and the general procedure for formation of nucleotide prodrugs begins with Example 4 on page 107. [Chabala Decl. ¶ 15]

A person of ordinary skill in the art would not find claim 150 to be indefinite, particularly in view of the specification and their own knowledge of the art. Therefore, the Applicants respectfully submit that claim 150 is definite and request withdrawal of the rejection.

VII. THE 35 USC § 101 REJECTION (POINT 13)

Claim 150 remains rejected under 35 USC § 101 because the Examiner says it is an improper process claim. This rejection is respectfully traversed.

The Examiner says:

> Applicants point to a Mitsunobo reaction on page 94 and Examples 1 and 4 as defining their synthetic process. They argue that these reagents and conditions are the steps required by 35 U.S.C. 101. This is not persuasive. The claims measure the invention. The U.S. Court of Customs and Patent Appeals wrote *In re Priest*, 199 USPQ 11 "We have consistently held that no applicant should have limitations of the specification read into a claim where no express statement of the limitation is included in the claim." (citations omitted) The steps of a chemical process are the reagents and reactions required to affect the chemical transformation. All Applicants have done is label what is the starting material and what is the product. No chemical steps are to be found in the claim. (Office Action p. 18)

There is no requirement that process claims contain steps. The Applicants believe that the claim is a proper process claim and that the 35 USC § 101 rejection is improper. 35 USC § 101 clearly allows the patenting of processes, machines, manufactures, and compositions of matter. Claim 150 is clearly a process claim. In fact, Dr. Chabala clearly understands that transforming is a step. [Chabala Decl. ¶ 15]. Therefore, the Applicants respectfully request withdrawal of the rejection that claim 150 is an improper process claim under 35 USC § 101.

VIII. CONCLUSION

In conclusion, Applicants respectfully submit that all pending claims are in condition for allowance. The Examiner is invited to contact Applicants' undersigned Representative if it is believed that prosecution may be furthered thereby.

Respectfully Submitted,

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